VERMONT

# Office of Vermont Health Access

## *Therapeutic Class Review*
## Urinary Antispasmodics

**Overview/Summary**

Approximately 13 million Americans suffer from urinary incontinence.[1] It is one of the most common problems in persons above 65 years of age, and is estimated to affect 15% to 30% of the elderly in the community setting and greater than 50% of those in the long-term care setting. Urinary incontinence is frequently cited as the reason for institutionalization of the elderly. Overactive bladder (OAB) is the most common type of incontinence.[1-3] OAB is the involuntary loss of urine associated with a sudden or overwhelming need to void and is frequently caused by the involuntary contraction of the detrusor before the bladder is full. The impact of urinary incontinence can have medical and economic consequences, including increased morbidity, falls, skin infections, social isolation, and increased healthcare utilization. An estimated $1.1 billion is spent every year on disposable products for adults.[1]

Urinary Antispasmodics include short-acting oxybutynin and flavoxate as well as long-acting tolterodine, darifenacin, solifenacin, and trospium. Oxybutynin, tolterodine, darifenacin and trospium are available as once daily extended-release formulations. Oxybutynin, oxybutynin XL, and flavoxate are available generically. Oxybutynin is also available as a transdermal formulation. All urinary antispasmodics, with the exception of flavoxate, are Food and Drug Administration (FDA)-approved for the treatment of overactive bladder.[4-12] In addition, oxybutynin XL is indicated for the treatment of detrusor overactivity and oxybutynin may be used for neurogenic bladder.[6-7] Flavoxate is not commonly used in the United States. It is indicated for the symptomatic relief of dysuria, urgency, nocturia, suprapubic pain, frequency and incontinence secondary to cystitis, prostatitis, urethritis, or urethrocystitis/urethrotrigonitis.[13] There are several off-label indications associated with urinary antispasmodics.[13] Oxybutynin may be used for refractory hot sweats and postoperative pain related to an indwelling catheter while trospium has been studied in patients with interstitial cystitis, brachytherapy-related OAB symptoms, pediatric bladder instability, and disorders of the gastrointestinal tract.

Urinary antispasmodics belong to a class of anticholinergic compounds known as muscarinic receptor antagonists.[1-12] These agents relax smooth muscle tissue located in the bladder, consequently decreasing bladder contractions. Overactive bladder (OAB) is believed to be caused by unstable detrusor muscle function. Since muscarinic receptors are found in many different organs, urinary antispasmodics are associated with adverse anticholinergic effects, such as blurred vision, dry mouth, constipation, urinary retention, and central nervous system effects such as dizziness, somnolence, and headaches. Extended-release formulations are associated with a lower frequency of anticholinergic adverse effects.[2,3] In addition, oxybutynin transdermal patch has demonstrated comparable efficacy to the immediate-release formulation with half its incidence of dry mouth. Unlike other agents, trospium, a quaternary ammonium compound, is water soluble and has demonstrated low penetration through the blood brain barrier and the gut.[2-5] Consequently trospium may cause less CNS and GI adverse effects.

Clinical practice guidelines recommend urinary antispasmodics as first line pharmacological therapy of OAB.[14-17] Head-to-head studies have established similar effectiveness across the class. However, no direct comparison studies with trospium have been performed to date. Extended-release oxybutynin and tolterodine may be better tolerated than their short-acting counterparts. In general, selection of optimal therapy should be guided by considerations of cost and tolerability. Urinary antispasmodics should not be used in patients with urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, or in those who are at risk for these conditions.[4-12,18]

## Medications

**Table 1. Medications Within Class Review**

| Generic Name (Trade name) | Medication Class | Generic Availability |
|---|---|---|
| *Short-Acting Agents* | | |
| Oxybutynin (Ditropan®) | Urinary Antispasmodic | ✔ |
| Flavoxate (Urispas®) | Urinary Antispasmodic | ✔ |
| *Long-Acting Agents* | | |
| Darifenacin (Enablex®) ER | Urinary Antispasmodic | - |
| Oxybutynin XL (Ditropan XL®) | Urinary Antispasmodic | ✔ |
| Oxybutynin transdermal (Oxytrol®) | Urinary Antispasmodic | - |
| Solifenacin (Vesicare®) | Urinary Antispasmodic | - |
| Tolterodine (Detrol®) | Urinary Antispasmodic | - |
| Tolterodine LA (Detrol LA®) | Urinary Antispasmodic | - |
| Trospium (Sanctura®) | Urinary Antispasmodic | - |
| Trospium XR (Sanctura XR®) | Urinary Antispasmodic | - |

## Indications

**Table 2. Food and Drug Administration Approved Indications[4-12]**

| Generic Name | Treatment of OAB | Treatment of detrusor overactivity | Neurogenic bladder | Symptomatic relief of symptoms of cystitis, prostatitis, urethritis, or urethrocystitis/urethrotrigonitis |
|---|---|---|---|---|
| *Short-Acting Agents* | | | | |
| Oxybutynin | ✔ * | | ✔ | |
| Flavoxate | | | | ✔ |
| *Long-Acting Agents* | | | | |
| Darifenacin ER | ✔ | | | |
| Oxybutynin XL | ✔ * | ✔ † | | |
| Oxybutynin transdermal | ✔ | | | |
| Solifenacin | ✔ * | | | |
| Tolterodine IR/LA | ✔ * | | | |
| Trospium IR/XR | ✔ * | | | |

OAB=overactive bladder
* In patients with symptoms of urge urinary incontinence, urgency, and urinary frequency
† In pediatric patients ≥6 years of age with symptoms of detrusor overactivity, associated with a neurological condition.

Potential off-label uses for oxybutynin include refractory hot sweats and postoperative pain related to an indwelling catheter. Trospium has been studied in patients with interstitial cystitis, brachytherapy-related OAB symptoms, pediatric bladder instability, and disorders of the gastrointestinal tract.

## Pharmacokinetics

**Table 3. Pharmacokinetics[4-13,18]**

| Generic Name | Absorption (%) | Renal Excretion (%) | Metabolism | Active Metabolites | Serum Half-Life (hours) |
|---|---|---|---|---|---|
| Oxybutynin IR/XR | 6-10.9 | <0.1 | Liver, CYP3A4 | N-desethyloxybutynin | 1-2/12 |
| Oxybutynin transdermal | 6 | <0.1 | Liver, CYP450 | N-desethyloxybutynin | 7-8 |
| Flavoxate | No Data | 57 | No Data | Methyl flavone carboxylic acid | No Data |

| | | | | | |
|---|---|---|---|---|---|
| Darifenacin ER | 15-25 | 60 | Liver, CYP2D6 and 3A4 | No Data | 13-19 |
| Solifenacin | 90 | 70 | Liver, CYP3A4 | 4R-hydroxy solifenacin | 45-68 |
| Tolterodine IR/LA | 77 | 77 | Liver, CYP2D6 and 3A4 | 5-hydroxymethyl | 2/7 |
| Trospium IR/XR* | 9.6 | 5.8 | Ester hydrolysis | None | 20/35 |

* CYP450 does not contribute significantly to the elimination of trospium

**Clinical Trials**

With the exception of trospium extended release formulation, all the urinary antispasmodic agents have been evaluated in head-to-head studies. In two, 12-week, randomized, double-blind, placebo-controlled trials (N=1,165) enrolling patients with overactive bladder with symptoms of urinary frequency, urgency, and urge urinary incontinence, trospium XR was associated with a statistically significant reduction in urinary frequency, incontinence episodes, and increases in void volume. Of note, significant reduction in incontinence episodes occurred by week-1 of therapy initiation ($P$<0.001). CNS effects, such as headache, were more frequently reported by patients receiving placebo than active therapy.

Halaska et al. found immediate-release trospium comparable to oxybutynin in terms of efficacy in 358 patients with OAB.[21] Treatment-related adverse effects were more common with oxybutynin vs. trospium therapy ($P$<0.01). Three short-term studies evaluated the safety and efficacy of oxybutynin compared with darifenacin.[22-24] There was no significant difference in efficacy between the two regimens. However, oxybutynin was associated with a greater frequency of dry mouth; while more patients receiving darifenacin reported constipation. Moreover, three studies evaluated the safety and efficacy of the immediate- and the extended-release oxybutynin formulations.[25-27] Likewise, there was no significant difference in efficacy between the two oxybutynin formulations. Dry mouth was the most frequently reported side-effect in both groups.

Extended-release oxybutynin and tolterodine were directly compared in two large randomized controlled trials, OPERA and OBJECT.[28,30] In the OPERA study (N=790), both regimens were associated with similar improvements in OAB symptoms; while dry mouth was more common in patients receiving oxybutynin XL ($P$=0.02).[28,29] In contrast, the OBJECT study (N=378) found oxybutynin XL superior to tolterodine LA in several efficacy parameters with comparable adverse effects.[30] Several studies evaluating the immediate-release oxybutynin and tolterodine formulations found both comparable in terms of effectiveness in adults and children with OAB or detrusor instability.[32,34,35] Oxybutynin was associated with a greater incidence of adverse effects than tolterodine. A meta-analysis by Harvey et al. found a 46% reduction in the risk of dry mouth with tolterodine therapy vs. oxybutynin.[35] In two studies, the transdermal formulation of oxybutynin demonstrated comparable efficacy to oxybutynin IR and tolterodine IR, with a lower incidence of adverse effects than either of the oral agents.[36,37] Moreover, the STAR study (N=1,177) did not find a statistically significant difference in safety or efficacy endpoints between solifenacin and tolterodine LA.[39,40] Finally, two meta-analyses identified oxybutynin IR with the greatest risk for adverse effects compared to the other urinary antispasmodics.[41,42] While all agents were more effective than placebo, oxybutynin and solifenacin were associated with greatest efficacy in head-to-head studies. Table 4 presents published head-to-head clinical studies evaluating the safety and efficacy of urinary antispasmodics.

**Table 4. Clinical Trials**[19-42]

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| ***Trospium ER vs. placebo*** | | | | |
| Dmochowski et al[19]<br><br>Trospium chloride extended release 60mg DAILY<br><br>vs.<br><br>placebo | RCT, DB, PC, PG, MC<br><br>Patients 18 years or older with OAB for 6 months or longer, with symptoms of urinary frequency, urgency, and urgency urinary incontinence (UUI) | N=564<br><br>12 Weeks | Primary:<br>Change in the mean number of daily toilet voids and the number of UUI episodes<br><br>Secondary:<br>Urgency severity, volume voided per void, dry rate (defined as no UUI episodes during the diary collection period, responder rate (≤8 toilet voids/day and no UUI episodes), and adverse effects | Primary:<br>Treatment with trospium DAILY resulted in a significant reduction from baseline in the mean number of toilet voids per day compared with placebo at week-12 (19.3% vs. 13.1%; *P*<0.05).<br><br>At week-12, participants treated with trospium DAILY experienced a statistically significant reduction from baseline in daily UUI episodes compared with patients randomized to placebo (58.9% vs.37.1%; *P*<0.001).<br><br>Secondary:<br>Treatment with trospium DAILY resulted in a significant reduction from baseline in the mean urgency severity associated with toilet voids compared with placebo at week-12 (*P*<0.001).<br><br>Treatment with trospium DAILY resulted in a significant increase in the mean volume voided per void from baseline compared with placebo at week-12 (*P*<0.01).<br><br>A significantly greater proportion of patients treated with trospium DAILY were “dry” during the diary collection period compared with patients randomized to placebo (*P*<0.05).<br><br>A significantly greater proportion of patients treated with trospium DAILY responded to therapy compared with |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | patients randomized to placebo (*P*<0.05).<br><br>Treatment-related adverse effects occurred in 55% of trospium-treated patients and 45.8% of patients receiving placebo. Dry mouth occurred in 12.9% of subjects treated with trospium DAILY vs. 4.6% of those receiving placebo. Constipation occurred in 7.5% of those given trospium DAILY vs. 1.8% in the placebo group. CNS effects, such as headache, occurred in 1.8% of those given trospium DAILY vs. 2.1% in the placebo group. |
| Staskin D et al[20]<br><br>Trospium chloride extended release 60mg DAILY<br><br>vs.<br><br>placebo | RCT, DB<br><br>Men and women 18 years or older with symptoms of OAB for 6 months or greater | N=601<br><br>12 Weeks, 9 months open-label phase | Primary:<br>Calculated changes in daily urinary frequency and daily urgency urinary incontinence (UUI) episodes<br><br>Secondary:<br>Normalization rate (defined as no UUI episodes and a daily void frequency of 8 or fewer), urgency severity, volume voided per void, the number of urgency voids per day, and adverse effects | Primary:<br>Treatment with trospium DAILY resulted in a significant improvement in daily urinary frequency from baseline compared with placebo at week-12 (*P*<0.01).<br><br>Treatment with trospium DAILY resulted in a significant reduction in daily UUI episodes from baseline compared with placebo at week-12 (*P*<0.001).<br><br>Subjects treated with trospium DAILY experienced an average decrease in daily voids from 12.8 per day at baseline to fewer than 10 at week 12 (*P*<0.001).<br><br>Participants treated with trospium DAILY experienced an average decrease from 4.1 UUI episodes per day at baseline to 1.6 at week 12 (*P*<0.01).<br><br>Secondary:<br>Twice as many subjects treated with trospium DAILY |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | achieved normalization at week-12 compared with those given placebo (20.5% vs. 11.3%, *P*<0.01)<br><br>Treatment with trospium DAILY resulted in a significant improvement in daily urgency severity, volume voided per void, and the number of urgency voids per day compared with placebo at week-12 (*P*<0.01).<br><br>Dry mouth occurred in 8.7% of subjects treated with trospium DAILY vs. 3.0% of those receiving placebo. Constipation occurred in 9.4% of those given trospium DAILY vs. 1.3% in the placebo group. CNS effects, such as headache, occurred in 1% of those given trospium DAILY vs. 2.6% in the placebo group. |
| ***Trospium vs. Oxybutynin*** | | | | |
| Halaska et al[21]<br><br>Trospium chloride 20mg BID<br><br>vs.<br><br>oxybutynin 5 mg BID | RCT, DB, MC<br><br>Patients ≥18 years of age, with urge syndrome, urge incontinence as a component of mixed incontinence, or urge incontinence due to a neurological condition | N=358<br><br>52 Weeks | Primary:<br>Maximum cystometric bladder capacity<br><br>Secondary:<br>Change in the volume at the first sensation to void, volume at first unstable contraction, micturition frequency, subjective physician appraisal of efficacy, and adverse effects | Primary:<br>Both treatment groups experienced a significant improvement in the maximum cystometric bladder capacity from baseline (*P*=0.001). The change in bladder capacity was comparable between groups (*P* value not reported).<br><br>Secondary:<br>There were no statistically significant differences between groups in the volume at the first sensation to void, volume at first unstable contraction, or micturition frequency (*P* value not reported).<br><br>After 52 weeks of treatment, trospium and oxybutynin were associated with “cure” by 29% and 17% of |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | physicians, respectively (*P* value not reported).<br><br>Dry mouth occurred in 33% of patients treated with trospium vs. 50% of those receiving oxybutynin. Gastrointestinal adverse effects occurred in 39% of those given trospium vs. 51% in the oxybutynin group. CNS effects, such as headache, occurred in 4% of those given trospium vs. 9% in the oxybutynin group.<br><br>Treatment-related adverse effects occurred more frequently in patients receiving oxybutynin therapy compared to the trospium group (*P*<0.01).<br><br>The weekly risk of experiencing an adverse event was 0.027 with trospium and 0.045 with oxybutynin therapy. |
| ***Oxybutynin vs. Darifenacin*** | | | | |
| Chapple et al[22]<br><br>(Cohort 1):<br><br>Darifenacin IR 2.5 mg TID<br><br>vs<br><br>oxybutynin 2.5 mg TID<br><br>(Cohort 2):<br><br>darifenacin CR 15 mg DAILY | RCT, DB, DD, XO<br><br>Patients 18-75 years of age, with detrusor overactivity within 6 months, either idiopathic or neurogenic (secondary to a neurological lesion present for ≥12 months), with ≥2 associated symptoms (average of ≥7 | N=65<br><br>21 days | Primary:<br>Ambulatory urodynamics, responder rate (patients achieving 25-30% improvement), salivary flow, adverse effects<br><br>Secondary:<br>Not reported | Primary:<br>All treatment groups experienced a significant improvement in urodynamic pressure parameters (*P* value not reported).<br><br>There was no statistically significant difference between groups in the percentage of patients responding to therapy (*P* value not reported).<br><br>Oxybutynin treatment groups experienced a greater decrease in salivary flow compared to patients receiving darifenacin CR 15 DAILY (*P*<0.001) or darifenacin CR 30 mg therapy (*P* value not reported). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| vs<br><br>oxybutynin 5 mg TID<br><br>(Cohort 3):<br><br>darifenacin CR 30 mg DAILY<br><br>vs<br><br>oxybutynin 5 mg TID | micturitions/day, ≥7 episodes of urgency/week, ≥1 urge incontinence episode/week necessitating change of clothing or pads) | | | Dry mouth and constipation were the most frequently reported adverse effects. Within each of the three cohorts, patients receiving oxybutynin reported dry mouth more frequently than patients on darifenacin therapy (*P* value not reported). In contrast, constipation was reported more often by patients taking darifenacin therapy.<br><br>Secondary:<br>Not reported |
| Kay et al[23]<br><br>Darifenacin CR 7.5 mg DAILY for two weeks, titrated up to 15 mg DAILY<br><br>vs<br><br>oxybutynin ER 10 mg DAILY for one week, subsequently titrated up to 15 mg for one week and 20 mg for another week<br><br>vs<br><br>placebo | RCT, DB, DD, PC, PG, MC<br><br>Healthy patients aged >60 years | N=150<br><br>3 weeks | Primary:<br>Recall on the name-face association test, first-last name association test, misplaced objects test at week-3, adverse effects<br><br>Secondary:<br>Not reported | Primary:<br>In terms of name-face delayed recall, oxybutynin ER therapy was associated with significantly greater memory deterioration compared with both placebo and darifenacin CR therapy (*P*<0.05).<br><br>In terms of first-last name recall, darifenacin CR was comparable with placebo while oxybutynin ER therapy was associated with significantly greater memory deterioration than placebo (*P*<0.05).<br><br>In terms of object recall, darifenacin CR was comparable with placebo while oxybutynin ER therapy was associated with significantly greater memory deterioration than placebo (*P*<0.05).<br><br>Dry mouth and constipation were the most frequently reported adverse effects. Dry mouth occurred in 13 patients treated with darifenacin CR vs. 20 patients on |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | oxybutynin ER and 6 patients receiving placebo. Constipation was reported by 10 patients treated with darifenacin CR vs. 2 patients on oxybutynin ER and 1 patient receiving placebo. In general, treatment-related adverse effects occurred in 26 patients treated with darifenacin CR vs. 22 patients on oxybutynin ER and 16 patients receiving placebo.<br><br>Secondary:<br>Not reported |
| Zinner et al[24]<br><br>Darifenacin CR 15 mg DAILY for two weeks<br><br>vs<br><br>darifenacin CR 30 mg DAILY for two weeks<br><br>vs<br><br>oxybutynin 5 mg TID for two weeks<br><br>vs<br><br>placebo for two weeks | RCT, DB, PC, XO<br><br>Patients aged 18-85 years, with urge incontinence and urinary frequency | N=76<br><br>8 weeks | Primary:<br>Change in the number of daily incontinence episodes, severity of urgency episodes, frequency of urgency episodes and micturition, side effects<br><br>Secondary:<br>Not reported | Primary:<br>All treatment groups exhibited statistically significant improvements in the mean weekly number of incontinence episodes, mean daily number of urgency episodes, and severity of urgency episodes, compared to placebo ($P$<0.05).<br><br>Only darifenacin 30 mg daily was associated with a statistically significant reduction in the frequency of micturition compared to placebo ($P$<0.05).<br><br>Treatment-related adverse effects were mild-moderate. Darifenacin 15 mg daily was associated with a statistically significant reduction in the incidence of dry mouth compared to both darifenacin 30 mg DAILY and oxybutynin 5 mg TID regimens ($P$<0.05).<br><br>Darifenacin 30 mg DAILY was associated with statistically significant increase in the incidence of constipation compared to oxybutynin 5 mg TID ($P$<0.05). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | The only patients to experience blurred vision or dizziness were those randomized to the oxybutynin group; however, the difference with placebo was not statistically significant (*P*>0.05).<br><br>Secondary:<br>Not reported |
| ***Oxybutynin vs. Oxybutynin XL*** | | | | |
| Anderson et al[25]<br><br>Oxybutynin CR 5 mg DAILY, titrated up in 5 mg/day increments to 30 mg daily<br><br>vs<br><br>oxybutynin IR 5 mg once to four times daily | RCT, AC, DB, PG, MC<br><br>Patients aged 34-76 years, with urge incontinence or mixed incontinence with a primary urge component, with ≥6 urge incontinence episodes weekly (not on medication), previously responsive to oxybutynin therapy | N=105<br><br>Study duration not specified | Primary:<br>Change in the number of mean weekly urge incontinence episodes<br><br>Secondary:<br>Proportion of patients achieving resolution of urge incontinence episodes, number of incontinence episodes, proportion of those patients achieving continence and total void frequency, side effects | Primary:<br>The number of weekly urge incontinence episodes decreased from 27.4 to 4.8 with oxybutynin CR and from 23.4 to 3.1 with oxybutynin IR therapy (*P*=0.56).<br><br>Secondary:<br>Of the participants, 52% of patients randomized to oxybutynin CR and 51% of patients in the oxybutynin IR group experienced resolution of urge incontinence (*P*=0.7).<br><br>The total number of incontinence episodes decreased from 29.3 to 6 with oxybutynin CR and from 26.3 to 3.8 with oxybutynin IR therapy (*P*=0.6).<br><br>Continence was achieved in 41% of the oxybutynin CR and 40% of the oxybutynin IR group (*P*=0.9).<br><br>Normal void frequency increased by 54% in the oxybutynin CR and 17% in the oxybutynon IR group (*P*<0.001). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | Dry mouth of any severity was reported by 68% of patients receiving oxybutynin CR and 87% of the oxybutynin IR group (*P*=0.04). Moderate or severe dry mouth occurred in 25% and 46%, respectively (*P*=0.03). Both regimens were associated with comparable incidences of somnolence, blurred vision, constipation, dizziness, impaired urination, nervousness, and nausea (*P*>0.05). |
| Barkin et al[26]<br><br>Oxybutynin CR 15 mg DAILY, titrated up in 5 mg increments<br><br>vs<br><br>oxybutynin IR 5 mg TID, titrated up in 5 mg increments | RCT, AC, DB, MC<br><br>Patients ≥18 years with urge urinary incontinence | N=125<br><br>9 weeks | Primary:<br>Change in the number of mean weekly incontinence episodes, voluntary micturition, volume of urine voided per micturition, frequency and severity of urgency, side effects<br><br>Secondary:<br>Not reported | Primary:<br>There was no statistically significant difference between the two treatment groups in the number of incontinence episodes per week (*P*=0.404), voluntary micturition (*P*=286), volume of urine voided per micturition (*P*=0.533), frequency of urgency (*P*=0.116), or severity of urgency (*P*=0.255).<br><br>Both oxybutynin CR and IR groups exhibited statistically significant improvements from baseline in the number of mean weekly incontinence episodes, voluntary micturition, frequency and severity of urgency (*P*<0.001).<br><br>Dry mouth was the most frequently reported side effect in both treatment groups. Dry mouth was reported by 68% of patients receiving oxybutynin CR and 72% of the oxybutynin IR group (*P* value not reported). Headache was reported by 12% of patients receiving oxybutynin CR and 22% of the oxybutynin IR group (*P* value not reported). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | Secondary:<br>Not reported |
| Versi et al[27]<br><br>Oxybutynin CR 5 mg DAILY, titrated up in 5 mg/day increments every 7 days to a maximum of 20 mg daily<br><br>vs<br><br>oxybutynin IR 5 mg DAILY, titrated up in 5 mg/day increments every 7 days to a maximum of 20 mg daily | RCT, DB, DM, PG, MC<br><br>Patients 59.2 years of age on average, with 7-45 urge incontinence episodes per week and ≥4 days of incontinence/week, and prior response to anticholinergic therapy | N=226<br><br>≤7 weeks | Primary:<br>Change in the number of mean weekly incontinence episodes, percentage of patients reporting the absence of urge incontinence, side effects<br><br>Secondary:<br>Not reported | Primary:<br>Both oxybutynin CR and IR regimens were associated with significant weekly reductions from baseline in urge urinary incontinence episodes (83% vs. 76%; *P*=0.36).<br><br>At equal doses, comparable proportions of patients in both treatment groups reported the absence of urge incontinence (*P*=0.85).<br><br>The incidence of dry mouth increased with dose in both groups. However, there was no difference in dry mouth rates between the oxybutynin CR and IR groups (47.7% vs. 59.1%; *P*=0.09).<br><br>Secondary:<br>Not reported |
| ***Oxybutynin vs. Tolterodine*** | | | | |
| Diokno et al[28]<br><br>OPERA Study<br><br>Oxybutynin ER 10 mg DAILY<br><br>vs<br><br>tolterodine ER 4 mg DAILY | RCT, DB, PG, MC<br><br>Women with overactive bladder, aged ≥18 years, with 21 to 60 urge urinary incontinence episodes per week and ≥10 voids per 24 hours; patients with mixed | N=790<br><br>12 weeks | Primary:<br>Change in the number of weekly urge urinary incontinence episodes<br><br>Secondary:<br>Change in the number of total incontinence episodes, percentage of patients reporting complete continence, micturition | Primary:<br>Oxybutynin ER and tolterodine ER regimens were associated with comparable weekly reduction from baseline in the number of urge urinary incontinence episodes (*P*=0.13).<br><br>Secondary:<br>Oxybutynin ER and tolterodine ER regimens were associated with comparable reduction from baseline in the number of total incontinence episodes (*P*=0.08). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | incontinence were eligible if urge episodes predominated | | frequency, side effects | Significantly greater percentage of patients treated with oxybutynin ER reported no urge urinary incontinence episodes at last observation from baseline, compared with the tolterodine ER group (23% vs. 16.8%; *P*=0.03).<br><br>Oxybutynin ER and tolterodine ER regimens were associated with comparable reduction from baseline in micturition frequency (*P*=0.05). However, when a weekly analysis was performed, oxybutynin was more effective compared to tolterodine in decreasing mean weekly micturation frequency (*P*<0.05).<br><br>Dry mouth was the most frequently reported adverse effect in each group. Dry mouth was reported more often by the oxybutynin ER group compared to the tolterodine ER-treated group (29.7% vs. 22.3%; *P*=0.02). None of the other side-effects differed between the groups. |
| Anderson, MacDiarmid et al[29]<br><br>OPERA Study<br><br>Oxybutynin ER 10 mg DAILY<br><br>vs<br><br>tolterodine ER 4 mg DAILY | RCT, DB, PG, MC, SA<br><br>Present study is a sub-analysis of the OPERA study, evaluating the safety and efficacy of oxybutynin ER vs. tolterodine ER in patients with and without a history of prior anticholinergic | N=790<br><br>12 weeks | Primary:<br>Change in the number of weekly urge urinary incontinence episodes<br><br>Secondary:<br>Change in the number of total incontinence episodes, percentage of patients reporting complete continence, micturition frequency, side effects | Primary:<br>Among patients previously treated with anti-cholinergic therapy, oxybutynin ER and tolterodine ER regimens were associated with comparable weekly reduction from baseline in the number of urge urinary incontinence episodes (*P*=0.306).<br><br>Among patients not previously treated with anti-cholinergic therapy, oxybutynin ER and tolterodine ER regimens were associated with comparable weekly reduction from baseline in the number of urge urinary incontinence episodes (*P*=0.663). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | use.<br><br>Women with overactive bladder, aged ≥18 years, with 21 to 60 urge urinary incontinence episodes per week and ≥10 voids per 24 hours; patients with mixed incontinence were eligible if urge episodes predominated | | | Secondary:<br>Among patients previously treated with anti-cholinergic therapy, oxybutynin ER and tolterodine ER regimens were associated with comparable reduction from baseline in the number of total incontinence episodes (*P*=0.086).<br><br>Among patients not previously treated with anti-cholinergic therapy, oxybutynin ER and tolterodine ER regimens were associated with comparable reduction from baseline in the number of total incontinence episodes (*P*=0.886).<br><br>Among patients previously treated with anti-cholinergic therapy, significantly greater percentage of patients treated with oxybutynin ER reported no urge urinary incontinence episodes at last observation from baseline, compared with the tolterodine ER group (23.6% vs. 15.1%; *P*=0.038).<br><br>Among patients not previously treated with anti-cholinergic therapy, percentages of patients reporting no urge urinary incontinence episodes at last observation were comparable in the oxybutynin ER and tolterodine ER groups (29.4% vs. 26.4%; *P*=0.495).<br><br>Among patients previously treated with anti-cholinergic therapy, oxybutynin ER and tolterodine ER regimens were associated with comparable reduction from baseline in mean weekly micturition frequency (26% vs. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | 23%; *P*=0.052).<br><br>Among patients not previously treated with anti-cholinergic therapy, oxybutynin ER was associated with a statistically significant reduction from baseline in mean weekly micturition frequency, compared with tolterodine ER (33% vs. 29%; *P*=0.035).<br><br>Dry mouth was the most frequently reported adverse effect in each group. Among patients previously treated with anti-cholinergic therapy, dry mouth was reported more often by the oxybutynin ER group compared to the tolterodine ER-treated group (32.2% vs. 19.2%; *P*=0.004). None of the other side-effects differed between the groups. |
| Appell et al[30]<br><br>OBJECT Study<br><br>Oxybutynin ER 10 mg DAILY for 12 weeks<br><br>vs<br><br>tolterodine ER 2 mg BID for 12 weeks | RCT, DB, PG, MC<br><br>Patients with overactive bladder, aged ≥18 years, with 7 to 50 urge urinary incontinence episodes per week and ≥10 voids per 24 hours; patients with mixed incontinence were eligible if urge episodes predominated; | N=378<br><br>12 weeks | Primary:<br>The number of urge incontinence episodes at week-12<br><br>Secondary:<br>Change in the number of total incontinence episodes, micturition frequency, side effects | Primary:<br>At 12-weeks, oxybutynin ER was significantly more effective than tolterodine ER in reducing the number of urge incontinence episodes from baseline (*P*=0.03).<br><br>Secondary:<br>At 12-weeks, oxybutynin ER was significantly more effective than tolterodine ER in reducing the number of total incontinence episodes from baseline (*P*=0.02).<br><br>At 12-weeks, oxybutynin ER was significantly more effective than tolterodine ER in reducing the mean weekly micturition frequency from baseline (*P*=0.02).<br><br>Both drugs were associated with statistically significant |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | patients were stratified by severity of overactive bladder symptoms | | | improvements in symptoms of overactive bladder from baseline (*P*<0.001).<br><br>Overall, 96.2% and 95.3% of patients on oxybutynin ER and tolterodine ER, respectively, experienced fewer incontinence episodes at week-12 compared to baseline.<br><br>Dry mouth was reported by 28.1% of patients in the oxybutynin ER group compared to the 33.2% in the tolterodine ER-treated group (*P*=0.32). None of the side-effects reported during the study period differed between the groups. |
| Armstrong et al[31]<br><br>Oxybutynin ER 10 mg DAILY<br><br>vs<br><br>tolterodine ER 4 mg once daily<br><br>vs<br><br>tolterodine IR 2 mg twice daily | MA<br><br>Present study is a MA of the OPERA and OBJECT studies.<br><br>Patients, aged ≥18 years, with overactive bladder, defined by urge urinary frequency, urgency, and frequency | N=1,168<br><br>12 weeks | Primary:<br>Adverse events<br><br>Secondary:<br>Not reported | Primary:<br>Gastrointestinal adverse events occurred in 41.8%, 36.3%, and 45.1% of patients receiving oxybutynin ER, tolterodine ER, and tolterodine IR therapy, respectively (*P* value not reported).<br><br>The most common digestive system event was dry mouth, occurring in 29.3%, 22.3%, and 33.2% of patients receiving oxybutynin ER, tolterodine ER, and tolterodine IR therapy, respectively (*P* value not reported).<br><br>Approximately 10% of all patients experienced a nervous system side effect. The incidence of nervous system side effects in the oxybutynin ER, tolterodine ER, and tolterodine IR groups was comparable (10.2% vs. 8.3% vs. 10.9%, respectively; *P* value not reported).<br><br>Most adverse events were mild or moderate in intensity. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | Severe drug-related adverse events occurred in 4.3%, 1.5%, and 2.6% of patients in the oxybutynin ER, tolterodine ER, and tolterodine IR groups, respectively.<br><br>The most common adverse event resulting in early discontinuation from the study was dry mouth, with 1.2%, 1.0%, and 1.6% of patients discontinuing in oxybutynin ER, tolterodine ER, and tolterodine IR groups, respectively (*P* value not reported).<br><br>Secondary:<br>Not reported |
| Mallone-Lee et al[32]<br><br>Oxybutynin 2.5 mg BID for 2 weeks, titrated up to 5 mg BID<br><br>vs<br><br>tolterodine 2 mg BID | RCT, DB, PG, MC<br><br>Patients ≥50 years of age, with symptoms of urinary frequency with urgency, and/or urge incontinence during a 2-week washout period | N=378<br><br>10 weeks | Primary:<br>Adverse effects<br><br>Secondary:<br>Voids per 24 hours, urge incontinence episodes per 24 hours, voided volume per each void, pads used in 24 hours | Primary:<br>Oxybutynin therapy was associated with a greater incidence of ≥1 adverse effects compared with tolterodine (81% vs. 69%; *P*=0.01).<br><br>Oxybutynin therapy was associated with a greater incidence of dry mouth compared with tolterodine (61% vs. 37%; *P*=0.01).<br><br>Significantly more patients in the oxybutynin group experienced severe adverse events compared with the tolterodine group (28% vs. 13%; *P*=0.0004).<br><br>Secondary:<br>At 10-weeks, both treatment groups were associated with comparable improvements from baseline in the number of daily voids (*P*=0.97). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | At 10-weeks, both treatment groups were associated with comparable improvements from baseline in the number of daily urge incontinence episodes (*P*=0.065).<br><br>At 10-weeks, both treatment groups were associated with comparable improvements from baseline in the volume voided in each void (*P*=0.90).<br><br>At 10-weeks, both treatment groups were associated with comparable improvements from baseline in the number of pads used per day (*P*=0.43).<br><br>There was no difference in the time to onset of action between the treatment groups (*P* value not reported). The maximal treatment effect on urge incontinence episodes and mean voided volume per void was achieved within 4 weeks in both treatment groups. The maximal effect on voiding frequency occurred within 4-10 weeks in each treatment group. |
| Sand et al[33]<br><br>Oxybutynin ER 10 mg DAILY for 12 weeks<br><br>vs<br><br>tolterodine 2 mg BID for 12 weeks | RCT, DB, PG, MC<br><br>Patients, 58 years of age on average, with overactive bladder, with 7 to 50 urge incontinence episodes per week and ≥10 voids per 24 hours; patients with mixed | N=315<br><br>12 weeks | Primary:<br>Urge incontinence episodes, total incontinence episodes, micturition frequency, adverse effects<br><br>Secondary:<br>Not reported | Primary:<br>At 12 weeks, oxybutynin ER therapy was associated with statistically significant reduction from baseline in urge incontinence and total incontinence episodes compared with tolterodine (*P*=0.03).<br><br>At 12-weeks, both treatment groups were associated with comparable improvements from baseline in micturition frequency episodes (*P*=0.272).<br><br>The incidences of adverse effects were not significantly |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | incontinence were eligible if urge episodes predominated | | | different between the two treatment groups (*P*>0.05).<br><br>Secondary:<br>Not reported |
| Kilic et al[34]<br><br>Oxybutynin 0.4 mg/kg daily, divided into three doses<br><br>vs<br><br>tolterodine 1 mg BID; patients <5 years of age received 0.1 mg/kg daily, divided into two doses | RCT<br><br>Children, 3 to 13 years of age, with evidence of detrusor instability | N=60<br><br>6 months | Primary:<br>Change in bladder capacity, bladder compliance, and detrusor pressure<br><br>Secondary:<br>Not reported | Primary:<br>Tolterodine therapy was associated with significant improvements in bladder capacity, bladder compliance, and detrusor pressure from baseline (*P*<0.001).<br><br>Oxybutynin therapy was associated with significant improvements in bladder capacity, bladder compliance, and detrusor pressure from baseline (*P*<0.001).<br><br>There were no significant differences between treatment groups in change from baseline in bladder capacity or bladder compliance (*P* value not reported).<br><br>There were no significant differences between treatment groups in the recovery from detrusor instability (*P* value not reported).<br><br>There were no significant differences between treatment groups in clinical response to therapy (*P*>0.05).<br><br>Tolterodine therapy was associated with a lower incidence of adverse events compared to oxybutynin therapy (*P*=0.027).<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Harvey et al[35]<br><br>Oxybutynin 2.5-5 mg TID<br><br>vs<br><br>tolterodine 1-2 mg BID | MA<br><br>RCT, DB studies evaluating tolterodine 1-2 mg twice daily and oxybutynin 2.5-5 mg TID among patients, aged ≥18 years, with urge urinary incontinence or frequency (>8 times daily), and urgency, or diagnosed with detrusor instability | 4 studies | Primary:<br>Change in the number of incontinence episodes per 24 hours, number of daily micturitions, and mean voided volume per micturition<br><br>Secondary:<br>Adverse effects | Primary:<br>Oxybutynin was associated with a statistically significant reduction from baseline in the number of incontinence episodes per 24 hours compared with tolterodine (Weighed Mean Difference [WMD], 0.41; 95% CI, 0.04 to 0.77; *P* value not reported).<br><br>There was no statistically significant difference between the two regimens in the reduction of micturition frequency from baseline (WMD, 0.0; 95% CI, -0.38 to 0.38; *P* value not reported).<br><br>Oxybutynin was associated with a statistically significant increase from baseline in the volume voided per micturition compared with tolterodine (WMD, 8.24; 95% CI, 2.38 to 14.11; *P* value not reported).<br><br>Secondary:<br>Tolterodine therapy was associated with a statistically significant 46% reduction in the risk of dry mouth compared with oxybutynin therapy (Relative Risk [RR], 0.54; 95% CI, 0.48 to 0.61; *P* value not reported).<br><br>Tolterodine therapy was associated with a statistically significant 37% reduction in the risk of withdrawing from the study secondary to adverse effects compared with oxybutynin therapy (RR, 0.63; 95% CI, 0.46 to 0.88; *P* value not reported). |
| ***Oxybutynin transdermal vs. Oxybutynin IR*** | | | | |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Davila et al[36]<br><br>Oxybutynin transdermal 1.3 mg daily, 2-4 patches applied twice weekly, in addition to placebo capsule administered 2-3 times daily<br><br>vs<br><br>oxybutynin IR 2.5 mg, 2 capsules administered 2-3 times daily, in addition to a 2-2-4 placebo patches applied twice weekly | RCT, DB, MC<br><br>Patients ≥18 years of age, with a history of urge or mixed urinary incontinence with a predominance of urge symptoms, ≥3 urge urinary incontinence episodes, and experienced symptomatic improvement after 6 weeks of oral oxybutynin therapy | N=76<br><br>6 weeks | Primary:<br>Change in the number of daily incontinence episodes, adverse effects<br><br>Secondary:<br>Not reported | Primary:<br>Both oxybutynin transdermal and oral formulations were associated with statistically significant reductions in the number of daily urinary incontinence episodes from baseline (66% vs. 72%; *P*<0.0001). There was no statistically significant difference between the treatment groups (*P*=0.9).<br><br>Dry mouth occurred more frequently in the oral oxybutnin groups compared with the transdermal treatment group (94% vs. 38%; *P*<0.001).<br><br>Of patients randomized to the transdermal oxybutynin therapy, 67% reported a reduction in dry mouth severity compared with previous oral therapy.<br><br>Secondary:<br>Not reported |
| ***Oxybutynin transdermal vs. Tolterodine ER*** | | | | |
| Dmochowski, Sand et al[37]<br><br>Oxybutynin transdermal 3.9 mg daily applied twice weekly, in addition to placebo capsule administered once daily<br><br>vs<br><br>tolterodine ER 4 mg DAILY, in addition to a placebo patch | RCT, DB<br><br>Patients ≥18 years of age, treated for overactive bladder, ≥4 urge urinary incontinence episodes, with either pure urge or a predominance of urge episodes, ≥24 | N=361<br><br>12 weeks | Primary:<br>Change in the number of daily urinary incontinence episodes, percentage of patients achieving complete continence, frequency of daily micturitions, average urinary volume per void, quality of life, adverse effects | Primary:<br>Oxybutynin patch was associated with a statistically significant reduction in the number of urinary incontinence episodes per day from baseline compared to placebo (75% vs. 50%; *P*=0.0137). The therapeutic effect was observed after two weeks of therapy and was maintained for the duration of the study.<br><br>Tolterodine LA was associated with a statistically significant reduction in the number of urinary incontinence episodes per day from baseline compared |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| applied twice weekly<br><br>vs.<br><br>placebo | voids, and an average urinary void volume ≤350 ml | | Secondary:<br>Not reported | to placebo (75% vs. 50%; *P*=0.0011).<br><br>Both treatment groups experienced comparable reductions from baseline in the number of urinary incontinence episodes per day (*P*=0.216).<br><br>A greater percentage of patients randomized to either oxybutynin patch or tolterodine LA experienced complete continence compared to placebo (39% vs. 38% vs. 22%; *P*=0.014).<br><br>Both treatment groups experienced comparable reductions from baseline in the frequency of micturitions per day (*P*=0.276).<br><br>Both treatment groups experienced comparable improvements from baseline in the average urinary volume per void (*P*=0.769). Both therapies results in increased urinary volume per void compared to placebo (*P*<0.01).<br><br>Both treatment groups were associated with comparable improvements from baseline in the overall Global Assessment of Disease State scores (*P*=0.186). Both therapies led to statistically significant improvements from baseline in Global Assessment of Disease State scores compared to placebo (*P*≤0.01).<br><br>More treatment-related adverse effects occurred with tolterodine LA compared with the transdermal oxybutynin |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | therapy (*P* value not reported). The most common treatment-related adverse events in the transdermal oxybutynin group were application site reactions, including erythema and pruritis.<br><br>Anticholinergic adverse effects (i.e. dry mouth, constipation) were the most common treatment-related adverse events reported in association with tolterodine LA therapy.<br><br>Secondary:<br>Not reported |
| ***Tolterodine vs. Solifenacin*** | | | | |
| Chapple, Rechberger et al[38]<br><br>Solifenacin 5-10 mg DAILY<br><br>vs<br><br>tolterodine 2 mg BID<br><br>vs<br><br>placebo | RCT, DB, MC<br><br>Patients ≥18 years of age, with symptoms of overactive bladder for at least 3 months, ≥8 daily voids and ≥3 daily urgency or incontinence episodes during 3-day voiding diary period | N=1,033<br><br>12 weeks | Primary:<br>Change in the mean number of urgency episodes and all incontinence and urge incontinence episodes<br><br>Secondary:<br>Change in the mean number of voids per 24 hours, volume voided per each void, adverse effects | Primary:<br>Solifenacin 5 mg and 10 mg groups experienced statistically significant reductions in the mean number of urgency episodes/24 hours compared to placebo (52% vs. 55% vs. 33%; *P*<0.001). While tolterodine therapy was also associated with reduction in the mean number of urgency episodes/24 hours, the change was not statistically different from placebo (38% vs. 33%; *P*=0.0511).<br><br>Solifenacin 5 mg and 10 mg groups experienced statistically significant reductions in the number of urge incontinence episodes/24 hours compared to placebo (65% vs. 63% vs. 40%; *P*<0.01). While tolterodine therapy was also associated with reduction in the number of urge incontinence episodes/24 hours, the change was not statistically different from placebo (58% |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | vs. 40%; *P*=0.239).<br><br>Solifenacin 5 mg and 10 mg groups experienced statistically significant reductions in the number of incontinence episodes/24 hours compared to placebo (59% vs. 47% vs. 29%; *P*<0.01). While tolterodine therapy was also associated with reduction in the number of incontinence episodes/24 hours, the change was not statistically different from placebo (59% vs. 29%; *P*=0.112).<br><br>Secondary:<br>Solifenacin 5 mg, 10 mg, and tolterodine groups experienced statistically significant reductions in the mean number of voids/24 hours compared to placebo (17% vs. 20% vs. 15% vs. 8%, respectively; *P*<0.05).<br><br>Solifenacin 5 mg, 10 mg, and tolterodine groups experienced statistically significant reductions in the mean volume voided per each void compared to placebo (25% vs. 29% vs. 20% vs. 9%, respectively; *P*<0.001).<br><br>Discontinuation rates due to adverse events were comparable with solifenacin 5 mg, 10 mg, tolterodine, and placebo groups (3.2% vs. 2.6% vs. 1.9% vs. 3.7%; *P* value not reported).<br><br>The incidence of dry mouth was lowest in the solifenacin 5 mg group and highest with solifenacin 10 mg therapy (14% vs. 21.3%; *P* value not reported). The incidence of |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | constipation was lowest in the tolterodine group and highest with solifenacin 10 mg therapy (2.6% vs. 7.8%; *P* value not reported). The incidence of blurred vision was lowest in the tolterodine group and highest with solifenacin 10 mg therapy (1.5% vs. 5.6%; *P* value not reported). |
| Chapple, Martinez-Garcia et al[39]<br><br>STAR Study<br><br>Solifenacin 5 mg DAILY, offered to titrate up to 10 mg DAILY after 4 weeks of therapy<br><br>vs<br><br>tolterodine ER 4 mg DAILY | RCT, DB, DD, PRO, PG<br><br>Patients ≥18 years of age, with symptoms of overactive bladder for at least 3 months, ≥8 daily micturitions or ≥1 daily urgency episodes during 3-day voiding diary period | N=1,177<br><br>12 weeks | Primary:<br>Change in the number of daily micturitions<br><br>Secondary:<br>Change in the number of urgency episodes, urge incontinence episodes, overall incontinence episodes, nocturia episodes, ≥50% resolution of incontinence episodes, complete continence, mean volume voided per micturition, incontinence pad utilization, adverse effects | Primary:<br>Solifenacin therapy was associated with a statistically significant reduction in micturition frequency from baseline compared with tolterodine ER (*P*=0.004).<br><br>Secondary:<br>Solifenacin therapy was associated with a statistically significant reduction in the number of urgency episodes from baseline compared with tolterodine ER (*P*=0.035).<br><br>Solifenacin therapy was associated with a statistically significant reduction in the number of urge incontinence episodes from baseline compared with tolterodine ER (*P*=0.001).<br><br>Solifenacin therapy was associated with a statistically significant reduction in the number of overall incontinence episodes from baseline compared with tolterodine ER (*P*=0.006).<br><br>Both treatment groups were associated with comparable reductions in nocturia episodes from baseline (*P*=0.73).<br><br>Of those patients who were incontinent at baseline, |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | approximately 74% and 67% solifenacin- and tolterodine ER-treated patients, respectively, experienced ≥50% resolution of their incontinence episodes (*P*=0.021).<br><br>A greater percentage of patients randomized to solifenacin experienced complete continence compared to tolterodine-treated patients (59% vs. 49%; *P*=0.006).<br><br>Solifenacin therapy was associated with a statistically significant increase in the mean volume voided per micturition compared with tolterodine ER (*P*=0.01).<br><br>Solifenacin therapy was associated with a statistically significant reduction in incontinence pad utilization from baseline compared with tolterodine ER (*P*=0.0023).<br><br>The most frequently reported adverse events in both groups were dry mouth, constipation, and blurred vision. Severe dry mouth occurred in 1.7% of solifenacin-treated patients and 1.5% of tolterodine ER-treated patients (*P* value not reported).<br><br>The rates of discontinuation due to adverse effects in the solifenacin and tolterodine ER groups were comparable (3.5% vs. 3%; *P* value not reported). |
| Chapple, Fianu-Jonsson et al[40]<br><br>STAR Study | RCT, DB, DD, PRO, PG, SA<br><br>Present study is a sub-analysis of the | N=1,177<br><br>4 weeks | Primary:<br>Change in the number of daily micturitions<br><br>Secondary: | Primary:<br>At week-4, both solifenacin and tolterodine ER therapies resulted in comparable reductions in micturition frequency from baseline (-1.71 vs. -1.47; *P*>0.05). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Solifenacin 5 mg DAILY<br><br>vs<br><br>tolterodine ER 4 mg DAILY | STAR study evaluating the safety and efficacy of solifenacin 5 mg and tolterodine ER 4 mg.<br><br>Patients ≥18 years of age, with symptoms of overactive bladder for at least 3 months, ≥8 daily micturitions or ≥1 daily urgency episodes during 3-day voiding diary period | | Change in the number of urgency episodes, urge incontinence episodes, overall incontinence episodes, nocturia episodes, complete continence, mean volume voided per micturition, incontinence pad utilization, adverse effects | Secondary:<br>At week-4, both solifenacin and tolterodine ER therapies resulted in comparable reductions in the number of urgency episodes from baseline (-1.98 vs. -1.67; *P*>0.05).<br><br>At week-4, both solifenacin and tolterodine ER therapies resulted in comparable reductions in the number of urge incontinence episodes from baseline (-1.22 vs. -0.91; *P*>0.05).<br><br>At week-4, solifenacin therapy was associated with a significant 44.4% reduction in the number of overall incontinence episodes from baseline compared to tolterodine ER (-1.30 vs. -0.90; *P*=0.0181).<br><br>Both treatment groups were associated with comparable reductions in nocturia episodes from baseline (*P*>0.05).<br><br>A greater percentage of patients randomized to solifenacin experienced complete continence compared to tolterodine-treated patients (39% vs. 34%; *P*>0.05).<br><br>At week-4, both solifenacin and tolterodine ER therapies resulted in comparable increases from baseline in the mean volume voided per micturition (*P*>0.05).<br><br>At week-4, both solifenacin and tolterodine ER therapies were associated with comparable reduction from baseline in incontinence pad utilization (-1.21 vs. -0.80; |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | *P*>0.05).<br><br>The most frequently reported adverse events in both groups were dry mouth, constipation, and blurred vision. Dry mouth occurred in 18.2% of solifenacin-treated patients and 14.5% of tolterodine ER-treated patients (*P* value not reported). The incidences of constipation were 3% vs. 1.2% and blurred vision 0.2% vs. 1.2% for the solifenacin and tolterodine ER groups, respectively.<br><br>The rates of discontinuation due to adverse effects in the solifenacin and tolterodine ER groups were comparable (3% vs. 2.8%; *P* value not reported). |
| ***Oxybutynin vs. Tolterodine vs. Trospium vs. Darifenacin vs. Solifenacin*** | | | | |
| Chapple, Khullar et al[41]<br><br>Oxybutynin IR 2.5-5 mg BID-QID<br><br>vs<br><br>oxybutynin ER 5-20 mg DAILY<br><br>vs<br><br>tolterodine IR 1-2 mg BID<br><br>vs | MA<br><br>Patients ≥18 years of age, with idiopathic overactive bladder, detrusor overactivity, urinary incontinence, mixed incontinence with predominantly urge incontinence, or urge urinary incontinence | 55 studies<br><br>2 weeks-18 months | Primary:<br>Total withdrawals, adverse effects<br><br>Secondary:<br>Efficacy measures | Primary:<br>All study medications, except oxybutynin IR, were associated with tolerability comparable to placebo (*P* value not reported). Oxybutynin IR was associated with a 40% greater risk of withdrawing from the study compared with placebo (*P* value not reported).<br><br>Compared with oxybutynin IR therapy, oxybutynin ER, tolterodine IR/ER were associated with lower risks of early therapy discontinuation (*P* value not reported).<br><br>Oxybutynin IR and oxybutynin patch formulation were the only drugs associated with early therapy discontinuation due to adverse effects. Tolterodine IR was associated with lower withdrawals due to side effects compared with oxybutynin IR. Tolterodine ER |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| tolterodine ER 2-4 mg DAILY<br><br>vs<br><br>trospium 20 mg BID<br><br>vs<br><br>darifenacin<br><br>vs<br><br>solifenacin 5-10 mg DAILY<br><br>vs<br><br>placebo | | | | was associated with lower withdrawals due to side effects compared with oxybutynin IR and oxybutynin patch.<br><br>Dry mouth was the most frequently reported side effect with all drugs. Oxybutynin IR was associated with a greater incidence of dry mouth compared with oxybutynin ER, oxybutynin patch, tolterodine ER, tolterodine IR, and trospium (*P* value not reported).<br><br>Secondary:<br>All agents were found efficacious compared with placebo (*P* value not reported).<br><br>In direct comparison trials, oxybutynin ER/IR and solifenacin were associated with greater efficacy compared to other urinary antispasmodics. |
| Hay-Smith et al[42]<br><br>Oxybutynin IR 2.5-5 mg BID-QID<br><br>vs<br><br>oxybutynin ER 5-20 mg DAILY<br><br>vs<br><br>tolterodine IR 1-2 mg BID | MA<br><br>Patients ≥18 years of age, with overactive bladder syndrome, detrusor overactivity, or symptoms of overactive bladder secondary to a neurologic disorder | N=11,332 (49 studies)<br><br>2 weeks-3 months | Primary:<br>Patient self-reported improvement or cure<br><br>Secondary:<br>The number of leakage episodes, the number of daily micturitions, withdrawal rate, adverse effects | Primary:<br>There were no statistically significant differences between oxybutynin and tolterodine groups in the proportion of patients reporting improvement or cure (44% vs. 47%; RR, 1.06; 95% CI, 0.89 to 1.26).<br><br>Secondary:<br>There were no statistically significant differences between oxybutynin and tolterodine groups in the number of reported leakage episodes (WMD, -0.15; 95% CI, -0.47 to 0.16).<br><br>There were no statistically significant differences |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| vs<br><br>tolterodine ER 2-4 mg DAILY<br><br>vs<br><br>trospium 20 mg BID<br><br>vs<br><br>placebo | | | | between oxybutynin and tolterodine groups in the number of daily micturitions (WMD, -0.25; 95% CI, -0.61 to 0.10).<br><br>Tolterodine was associated with lower withdrawals due to side effects compared with oxybutynin therapy (7% vs. 12%; RR, 0.57; 95% CI, 0.43 to 0.75).<br><br>Tolterodine was associated with 30-50% reduced risk of dry mouth compared with oxybutynin therapy (RR, 0.60; 95% CI, 0.54 to 0.66).<br><br>Trospium is associated with a lower risk of dry mouth compared with oxybutynin therapy (RR, 0.74; 95% CI, 0.59 to 0.93).<br><br>There were no statistically significant differences between oxybutynin IR or tolterodine IR and oxybutynin ER or tolterodine ER in the number of leakage episodes or daily micturitions (*P* value not reported). |

Drug regimen abbreviations: BID=twice daily, TID=three times daily, CR=controlled-release, ER/XL=extended-release, IR=immediate-release, LA=long-acting
Study abbreviations: AC=active-controlled, DB=double-blind, CI=confidence interval, DD=double-dummy, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SA=sub-analysis, WMD=weighted mean difference, XO=crossover
Miscellaneous: UUI=urgency urinary incontinence

## Special Populations

**Table 5. Special Populations[4-12]**

| Generic Name | Population and Precaution | | | | | |
|---|---|---|---|---|---|---|
| | Elderly/ Children | Renal dysfunction | Hepatic dysfunction | Pregnancy Category | Excreted in Breast Milk | Other |
| Oxybutynin | Safe and effective in children >5 years of age; Dose adjustment advised for elderly patients. | Caution advised | Caution advised | B | Unknown | Caution advised for patients with myasthenia gravis, or dementia (treated with cholinesterase inhibitors) |
| Oxybutynin XL | Safe and effective in children >6 years of age; no dosage adjustment required in elderly patients. | Caution advised | Caution advised | B | Unknown | Precautions same as for oxybutynin |
| Oxybutynin transdermal | Not studied in pediatric population; no dosage adjustment required in elderly patients. | Population not studied | Population not studied | B | Unknown | Precautions same as for oxybutynin |
| Flavoxate | Not studied in children <12 years of age | Population not studied | Population not studied | B | Unknown | |
| Darifenacin ER | Not studied in pediatric population; no dosage adjustment required in elderly patients | No dosage adjustment required | Dose adjustment for patients with moderate hepatic impairment; not studied in severe hepatic impairment and is not recommended in these patients | C | Unknown | |
| Solifenacin | Not studied in pediatric patients; no dosage | Dose adjustment for patients with severe renal | Dose adjustment for patients with moderate | C | Unknown | -Dose adjustment required for patients receiving potent CYP3A4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | adjustment required in elderly patients | impairment required. | hepatic impairment; not studied in severe hepatic impairment | | | inhibitors<br>-Caution in patients with a history of QT prolongation or taking drugs known to prolong QT interval |
| Tolterodine | Safety and efficacy not established in children; no dosage adjustment required in elderly patients | Dose adjustment for patients with severe renal impairment required | Dose adjustment required for patients with severe hepatic impairment | C | Unknown | -Caution advised for patients with myasthenia gravis<br>-Caution in patients with a history of QT prolongation or taking drugs known to prolong QT interval |
| Tolterodine LA | Safety and efficacy not established in children*; no dosage adjustment required in elderly patients | Dose adjustment for patients with severe renal impairment required | Dose adjustment required for patients with severe hepatic impairment. | C | Unknown | -Caution advised for patients with myasthenia gravis.<br>-Caution in patients with a history of QT prolongation or taking drugs known to prolong QT interval<br>-Proton Pump Inhibitors and antacids increase the rate of drug release. |
| Trospium | Not studied in pediatric patients; dosage adjustment in patients >75 years of age | Dose adjustment required for patients with severe renal impairment | Caution is advised in patients with moderate-severe hepatic dysfunction | C | Yes (animal studies); Unknown risk in humans | -Alcohol may enhance anticholinergic side effects (drowsiness) |
| Trospium XR | Not studied in pediatric patients; safe and effective in elderly patients† | Use not recommended for use in patients with creatinine clearance <30 ml/min | Caution is advised in patients with moderate-severe hepatic dysfunction | C | Yes (animal studies); Unknown risk in humans | - Alcohol should be avoided within 2 hours of use. |

GI=gastrointestinal
* Evaluated in 710 patients aged 5-10 years
† Higher incidence of adverse events reported in patients >65 years of age

**Adverse Drug Events**

The following table presents the most common adverse events reported with urinary antispasmodics in clinical trials. The most frequently reported adverse events with oral agents were dry mouth, constipation,

blurred vision, dizziness, and headache.[3-7,9-12] Application site reaction was the most common adverse event reported in association with transdermal oxybutynin formulation.[8]

**Table 6. Adverse Drug Events** [4-12]

| Adverse Event | Generic Name | Reported Frequency (%) |
|---|---|---|
| Dry mouth | Oxybutynin | 71.4 |
| | Oxybutynin XL | 61 |
| | Oxybutynin transdermal | 4.1-9.6 |
| | Flavoxate | ✔ |
| | Darifenacin ER | 18.7-35.3 |
| | Solifenacin | 10.9-27.6 |
| | Tolterodine | 35 |
| | Tolterodine LA | 23 |
| | Trospium | 20.1 |
| | Trospium XR | 10.7 |
| Constipation | Oxybutynin | 15.1 |
| | Oxybutynin XL | 13 |
| | Oxybutynin transdermal | 3.3 |
| | Flavoxate | - |
| | Darifenacin ER | 14.8-21.3 |
| | Solifenacin | 5.4-13.4 |
| | Tolterodine | 7 |
| | Tolterodine LA | 6 |
| | Trospium | 9.6 |
| | Trospium XR | 8.5 |
| Blurred vision | Oxybutynin | 9.6 |
| | Oxybutynin XL | 8 |
| | Oxybutynin transdermal | 2.5 |
| | Flavoxate | ✔ |
| | Darifenacin ER | - |
| | Solifenacin | 3.8-4.8 |
| | Tolterodine | 3 |
| | Tolterodine LA | 1 |
| | Trospium | ✔ |
| | Trospium XR | - |
| Dizziness | Oxybutynin | 16.6 |
| | Oxybutynin XL | 6 |
| | Oxybutynin transdermal | ✔ |
| | Flavoxate | ✔ |
| | Darifenacin ER | 0.9-2.1 |
| | Solifenacin | 1.8-1.9 |
| | Tolterodine | 5 |
| | Tolterodine LA | 2 |
| | Trospium | ✔ |
| | Trospium XR | - |
| Headache | Oxybutynin | 7.5 |
| | Oxybutynin XL | 6-10 |

| | | |
|---|---|---|
| | Oxybutynin transdermal | - |
| | Flavoxate | ✔ |
| | Darifenacin ER | 6.7 |
| | Solifenacin | ✔ |
| | Tolterodine | 7 |
| | Tolterodine LA | 6 |
| | Trospium | 4.2 |
| | Trospium XR | - |

**Contraindications / Precautions**
All urinary antispasmodics are contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, or at risk for these conditions.[4-12]

Urinary antispasmodics should be used with caution in patients with clinically significant bladder outflow obstruction, gastrointestinal obstructive disorders, or controlled narrow-angle glaucoma. In addition, urinary antispasmodics should be used with caution in patients with conditions such as ulcerative colitis, intestinal atony and myasthenia gravis. Moreover, tolterodine and solifenacin should be used with caution in patients who have a history of QT prolongation.

**Drug Interactions**
All urinary antispasmodics, except for trospium, are metabolized by the CYP450 (3A4/2D6) enzymes. Consequently, inhibitors of CYP450 may decrease their metabolism and lead to increased pharmacological and toxic effects. Trospium is the only agent within this class that does not undergo hepatic metabolism via CYP450 system and is consequently not associated with significant metabolic drug-drug interactions. Since trospium is excreted by the kidneys via tubular secretion and glomerular filtration, agents competing with trospium for tubular secretion may increase its plasma concentration and risk of toxicity. Moreover, specific drug interaction studies have not been performed with the transdermal oxybutynin product. Significant drug interactions with the urinary antispasmodics are listed in Table 7.

**Table 7. Drug Interactions**[5-10,13,18]

| Generic Name | Interacting Medication or Disease | Potential Result |
|---|---|---|
| Oxybutynin | Clomipramine | Oxybutynin may decrease the pharmacologic activity of clomipramine via induction of CYP3A4 metabolism. |
| Oxybutynin | Potent CYP3A4 inhibitors (itraconazole, ketoconazole, erythromycin, clarithromycin, miconazole) | Potent CYP3A4 inhibitors may increase the pharmacologic and adverse effects of oxybutynin. |
| Tolterodine | Potent CYP3A4 inhibitors (itraconazole, ketoconazole, erythromycin, cyclosporine, clarithromycin, miconazole, vinblastine) | Potent CYP3A4 inhibitors may increase the pharmacologic and adverse effects of tolterodine via inhibition of CYP3A4 metabolism (in slow CYP2D6 metabolizers). Patients receiving potent CYP3A4 inhibitors should not receive >2 mg of tolterodine daily. |
| Tolterodine | Drugs known to cause QT prolongation (propafenone, quinidine, amiodarone) | Drugs known to cause QT prolongation may lead to additive, potentially life-threatening QT interval prolongation if used concurrently with tolterodine. |
| Tolterodine | Warfarin | Concurrent use of tolterodine and warfarin may increase the risk of bleeding. |

| Generic Name | Interacting Medication or Disease | Potential Result |
|---|---|---|
| Solifenacin | Potent CYP3A4 inhibitors (ketoconazole, itraconazole, telithromycin, clarithromycin, saquinavir, ritonovir, indinavir, nelfinavir, nefazodone) | Potent CYP3A4 inhibitors may increase the pharmacologic and adverse effects of solifenacin. Patients receiving potent CYP3A4 inhibitors, such as ketoconazole, should not receive >5 mg of solifenacin daily. |
| Darifenacin | Tricyclic antidepressants [TCAs] (imipramine, desipramine) | Darifenacin may increase the pharmacologic and adverse effects of TCAs via inhibition of CYP2D6 metabolism. |
| Darifenacin | Thioridazine | Darifenacin may increase the pharmacologic and adverse effects of thioridazine via inhibition of CYP2D6 metabolism. |
| Darifenacin | Flecainide | Darifenacin may increase the pharmacologic and adverse effects of flecainide via inhibition of CYP2D6 metabolism. |
| Darifenacin | Potent CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, clarithromycin, nelfinavir, nefazodone) | Potent CYP3A4 inhibitors may increase the pharmacologic and adverse effects of darifenacin. Patients receiving potent CYP3A4 inhibitors, such as ketoconazole, should not receive >7.5 mg of darifenacin daily. |

**Dosage and Administration**

Oxybutynin, tolterodine and trospium extended release formulations as well as darifenacin and solifenacin are approved for once daily dosing. Tolterodine immediate release tablets are dosed twice daily; while, flavoxate and oxybutynin immediate release tablets may be used up to four times daily. Oxybutynin is available in a liquid dosage form and as a transdermal patch. Trospium should be administered on an empty stomach, at least one hour before a meal. The other agents in the class can be taken without regard to meals. The usual dosing regimens for the urinary antispasmodics are summarized in Table 8.

**Table 8. Dosing and Administration[4-13]**

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| Oxybutynin | Tablet/syrup: 5 mg two to three times daily; maximum, 5 mg four times daily.<br><br>Elderly: initial, 2.5 mg two to three times daily | Children ≥5 years:<br>Initial, 5 mg twice daily; maximum, 5 mg three times daily<br><br>Safety and efficacy in children <5 years of age have not been established. | Tablet:<br>5 mg<br><br>Syrup:<br>5 mg/5 mL |
| Oxybutynin XR | 5-10 mg once daily; maximum, 30 mg daily.<br><br>Should be swallowed whole and should not be chewed, divided, or crushed.<br><br>May be administered without regard to meals. | Children ≥6 years:<br>Initial, 5 mg once daily; maximum, 20 mg once daily<br><br>Safety and efficacy in children <6 years of age have not been established. | Extended Release Tablet:<br>5 mg<br>10 mg<br>15 mg |

| | | | |
|---|---|---|---|
| Oxybutynin transdermal | One patch applied twice weekly (every 3 to 4 days)<br><br>Should be applied to dry, intact skin on the abdomen, hip, or buttock. | Safety and efficacy in children have not been established. | Transdermal Patch:<br>3.9 mg/day |
| Flavoxate | 100-200 mg three to four times daily | Children ≥12 years:<br>100-200 mg three to four times daily<br><br>Safety and efficacy in children <12 years of age have not been established. | Tablet:<br>100 mg |
| Darifenacin ER | Initial, 7.5 mg once daily; maximum, 15 mg once daily<br>Dose should not exceed 7.5 mg daily when used with potent CYP3A4 inhibitors.<br><br>Not recommended for use in patients with severe hepatic impairment.<br><br>May be administered without regard to meals. | Safety and efficacy in children have not been established. | Extended Release Tablet:<br>7.5 mg<br>15 mg |
| Solifenacin | Initial, 5 mg once daily; maximum, 10 mg once daily<br><br>May be administered without regard to meals.<br><br>Doses >5 mg daily should be avoided in patients with severe renal impairment, moderate hepatic impairment, or in conjunction with potent inhibitors of CYP450.<br><br>Not recommended for patients with severe hepatic dysfunction. | Safety and efficacy in children have not been established. | Tablet:<br>5 mg<br>10 mg |
| Tolterodine | Initial, 2 mg twice daily (1 mg twice daily for patients with severe renal/hepatic impairment or if coadministered with potent inhibitors of CYP3A4) | Safety and efficacy in children have not been established. | Tablet:<br>1 mg<br>2 mg |
| Tolterodine LA | Initial, 4 mg once daily (2 mg once daily for patients with severe renal/hepatic impairment or if coadministered with potent inhibitors of CYP3A4) | Safety and efficacy in children have not been established. | Extended Release Capsule:<br>2 mg<br>4 mg |
| Trospium | Initial, 20 mg twice daily, administered on an empty | Safety and efficacy in children have not been | Tablet:<br>20 mg |

| | | | |
|---|---|---|---|
| | stomach, ≥1 hour before a meal.<br><br>The recommended dose for patients with severe renal impairment or patients ≥75 years of age is 20 mg once daily at bedtime. | established. | |
| Trospium XR | One 60 mg capsule daily in the morning, administered with water on an empty stomach, ≥1 hour before a meal.<br><br>Should not be used in patients with severe renal impairment. | Safety and efficacy in children have not been established. | Extended Release Capsule:<br>60 mg |

**Drug Acquisition Cost**

**Table 9. Drug Dosage Form (and MAC cost if applicable)**

| Medication | Dosage Form | Strength(s) | MAC Cost Per Unit† |
|---|---|---|---|
| Detrol® | Tablet | 1 mg, 2 mg | |
| Detrol LA® | Capsule | 2 mg, 4 mg | |
| Ditropan® | Tablet | 5 mg | |
| Ditropan XL® | Tablet | 5 mg, 10 mg, 15 mg | |
| Enablex® | Tablet | 7.5 mg, 15 mg | |
| Flavoxate | Tablet | 100 mg | $0.98† |
| Oxybutynin | Tablet | 5 mg | $0.107† |
| Oxybutynin XL | Tablet | 5 mg, 10 mg, 15 mg | $2.15-$2.42† |
| Oxytrol® | Patch | 3.9 mg | |
| Sanctura® | Tablet | 20 mg | |
| Sanctura XR® | Capsule | 60 mg | |
| Urispas® | Tablet | 100 mg | |
| Vesicare® | Tablet | 5 mg, 10mg | |

†MAC as of 1/9/2009

**Potential Advantages/ Potential Disadvantages/Unanswered Questions**

- Extended-release products may offer enhanced tolerability (less antimuscarinic side effects) compared to immediate-release agents.
- Due to difference in structure, Sanctura XR® may exhibit a lower incidence of CNS and GI adverse effects compared to other agents in the class.
- Oxybutynin transdermal patch has demonstrated comparable efficacy to the immediate-release oxybutynin with half its incidence of dry mouth.
- Products available for once-daily use may lead to an improved adherence compared to short-acting antispasmodics (administered 2-3 times daily).
- Flavoxate is not indicated for the treatment of overactive or neurogenic bladder. It may only be used for the relief of symptoms associated with cystitis, prostatitis, urethritis, or urethrocystitis/urethrotrigonitis.
- All agents in the class (with the exception of tiotropium) exhibit CYP450 drug interactions.
- Sanctura® and Sanctura XR® may interact with drugs eliminated via renal tubular secretion.
- Both Sanctura® and Sanctura XR® must be taken on an empty stomach while other agents in the class do not have associated dietary restrictions.
- Head-to-head studies with flavoxate and Sanctura XR® have not been performed.

**Other Key Facts**

- Sanctura XR® patent expires in 8/2010
- Sanctura® patent expires in 5/2009
- Enablex® patent expires in 3/2015
- Vesicare® patent expires in 11/2018
- Detrol® patent expires in 9/2012
- Detrol LA® patent expires in 9/2012

**Clinical Guidelines**

**Table 10. Clinical Guidelines** [14-17]

| Clinical Guideline | Recommendation(s) |
|---|---|
| The American College of Obstetricians and Gynecologists (ACOG): **ACOG Practice Bulletin: Urinary Incontinence in Women (2005)**[14] | • Anticholinergic medications, oxybutynin chloride and tolterodine, have been shown in randomized controlled clinical trials to exert a small beneficial effect in patients with urge incontinence.<br>• No significant difference between anticholinergic agents has been reported.<br>• The most common adverse effect with anticholinergic therapy is dry mouth. Other adverse effects are blurred vision, constipation, nausea, dizziness, and headache. |
| National Institute for Health and Clinical Excellence (NICE): **Urinary Incontinence: The Management of Urinary Incontinence in Women (2006)**[15] | • Oxybutynin IR generic should be offered to women with overactive bladder or mixed urinary incontinence as first-line therapy.<br>• If patients cannot tolerate oxybutynin IR, darifenacin, solifenacin, tolterodine, trospium, or an extended release or transdermal oxybutynin formulation should be considered.<br>• Patients should be counseled on adverse effects common with anticholinergic drug therapy.<br>• Flavoxate is not recommended for the treatment of urinary incontinence or overactive bladder in women.<br>• Imipramine is not recommended for the treatment of urinary incontinence or overactive bladder in women.<br>• Duloxetine is not recommended for first-line treatment of stress urinary incontinence. It may be offered as a second-line therapy for women who are not candidates for or opposed to surgical treatment of stress urinary incontinence.<br>• Desmopressin should be considered for the reduction of nocturia in women with urinary incontinence of overactive bladder.<br>• Systemic hormone replacement is not recommended for the treatment of urinary incontinence or overactive bladder in women.<br>• Intravaginal estrogens are recommended for the treatment of overactive bladder symptoms in postmenopausal women with vaginal atrophy. |
| European Association of Urology (EAU): **Guidelines on Neurogenic Lower Urinary Tract Dysfunction (2008)**[16] | • According to the guideline, anticholinergic agents are the most effective therapy for detrusor overactivity (Level of Evidence 1A; Grade of Recommendation A).<br>• Anticholinergic agents are used to reduce detrusor overactivity and to improve bladder compliance (Level of Evidence 1A; Grade of Recommendation A).<br>• Oxybutynin, trospium chloride, and tolterodine are safe and |

| | |
|---|---|
| | effective agents (Level of Evidence 1A; Grade of Recommendation A).<br>• Due to different tolerability profiles, patients experiencing an adverse effect or inadequate efficacy with one anticholinergic agent may be switched to another.<br>• Darifenacin and solifenacin have limited clinical data in patients with neurogenic bladder overactivity. |
| International Scientific Committee: **Evaluation and Treatment of Urinary Incontinence, Pelvic Organ Prolapse and Fecal Incontinence (2005)**[17] | • Antimuscarinic therapy is recommended for male patients with overactive bladder symptoms caused by detrusor overactivity (Grade C). These agents may be used in combination with an alpha-blocker.<br>• Antimuscarinic therapy is recommended for female patients with overactive bladder (Grade A). Initial regimen should be maintained for 8-12 weeks before re-assessing.<br>• Antimuscarinic therapy in adjunction to non-pharmacological therapy may be considered for elderly patients with urge urinary incontinence (Grade C). Medication should be initiated at a low dose and titrated up cautiously.<br>• Antimuscarinic therapy in adjunction to behavioral therapy is recommended for patients with neurogenic incontinence. |

**Conclusions**

Overactive bladder and urinary incontinence are common conditions primarily affecting the elderly. If left untreated, social, economic, and medical detriments may ensue. Urinary antispasmodics have demonstrated safety and efficacy in many clinical trials. Clinical practice guidelines do not acknowledge significant differences in efficacy between these agents. Currently, several immediate- and extended-release oral formulations are commercially available. In addition, oxybutynin is available as a transdermal patch formulation. While a limited number of head-to-head studies have been published, available literature suggests comparable efficacy. In addition, extended-release and transdermal formulations are associated with a lower incidence of dry mouth, a frequent anticholinergic adverse effect seen with urinary antispasmodic therapy. According to guidelines, patients experiencing an adverse effect on a short-acting antispasmodic may be switched to a longer-acting agent.

**Appendix I: Other Insurance Coverage**

| Managed Care Organization | Current Coverage |
|---|---|
| MassHealth (Massachusetts Medicaid) | Oxytrol requires PA; no PA required for other agents in the class |
| New Hampshire Medicaid | Detrol LA, Enablex, oxybutynin preferred<br><br>oxybutynin ER, Detrol, Ditropan XL, Ditropan, Oxytrol, Sanctura, Sanctura XR, Vesicare not preferred |
| New York Medicaid | Detrol LA, Enablex, oxybutynin, Oxytrol, Sanctura, Sanctura XR, Vesicare preferred<br><br>Ditropan, Ditropan XL, oxybutynin ER, Detrol not preferred |
| MVP Healthcare | Tier 1: flavoxate, oxybutynin IR/ER<br>Tier 2: Detrol, Detrol LA<br>Tier 3: Enablex, Ditropan XL, Ditropan, Oxytrol, Sanctura, Sanctura XR, Vesicare, Urispas |
| Cigna Healthcare | Tier 1: oxybutynin<br>Tier 2: Detrol, Detrol LA, Oxytrol, Vesicare<br>Tier 3: Ditropan XL, Ditropan, Enablex, Sanctura, Sanctura XR |
| Blue Cross Blue Shield of VT | Preferred Brands (Tier 2): Detrol, Oxytrol |

**Appendix II: Current Preferred/Non-Preferred Drug List (PDL) Alternatives (Long Acting)**

| Medication | Dosing Frequency | Net Cost/30 days |
|---|---|---|
| Enablex®, 7.5 mg, 15 mg extended release tablet (darifenacin) | 7.5-15 mg Daily | **$** |
| Detrol LA, 2, 4 mg tablet | 2 -4 mg Daily | **$$$$** |
| Oxybutynin XL, 5, 10, 15 mg extended release tablet | 5 - 30 mg Daily | **$$$** |
| Sanctura XR®, 60 mg capsule (trospium XR) | 60 mg Daily | **$** |
| Sanctura®, 20 mg capsule (trospium) | 20 mg BID | **$** |
| Vesicare® (solifenacin), 5 mg, 10 mg tablet | 5-10 mg Daily | **$** |

Drug regimen abbreviations: BID=twice daily

**Appendix III: Most Recent Utilization Within this Drug Class for OVHA:** April 1, 2008 to September 30, 2008

| Medication | Unique Members | # of Rx's | % Marketshare |
|---|---|---|---|
| Oxybutynin tab | 357 | 1,100 | 51.04 % |
| Detrol LA® | 81 | 313 | 14.52 % (29.67% of LA) |
| Oxybutynin XL | 105 | 303 | 14.06 % (28.72 % of LA) |
| Vesicare® | 50 | 189 | 8.77 % (17.91 % of LA) |
| Enablex® | 35 | 129 | 6.00 % (12.33 % of LA) |
| Sanctura® | 17 | 64 | 2.97 % (6.07 % of LA) |
| Detrol® | 10 | 38 | 1.76 % (3.60 % of LA) |
| Oxytrol® | 5 | 11 | 0.51 % (1.04 % of LA) |
| Sanctura XR® | 4 | 8 | 0.37 % (0.76 % of LA) |
| Class Total: | 664 | 2,155 | 100 % |

**Recommendations**

Currently, Vermont Medicaid requires prior authorization (PA) for all urinary antispasmodics (except short-acting oxybutynin). Oxybutynin is the preferred agent, available without a PA. Ditropan, flavoxate, Urispas, oxybutynin XL, Enablex, Sanctura, Sanctura XR and Vesicare are preferred long-acting agents, approved after an adequate trial of oxybutynin. Detrol, Detrol LA, Ditropan XL, and Oxytrol are non-preferred agents and require a trial of oxybutynin as well as two preferred long-acting agents. Patients ≥ 65 years of age are exempt from the short-acting oxybutynin trial requirement. Requests for any urinary antispasmodic agent (except Ditropan/Ditropan XL) may be approved for patients < 21 years of age without a PA. Patients < 21 years of age requesting Ditropan/Ditroapn XL must have an adequate trial of oxybutynin/oxybutynin XL. The following changes to the existing criteria are recommended.

- Oxybutynin XL moves to non-preferred after clinical criteria are met.

Ditropan, flavoxate, Urispas, Enablex, Sanctura, Sanctura XR, Vesicare

- The patient has had a documented side effect, allergy, or treatment failure with oxybutynin.

AND

- If a medication has an AB rated generic there must have also been a trial of the generic formulation.

Detrol, Detrol LA, oxybutynin XL, Ditropan XL

- The patient has had a documented side effect, allergy, or treatment failure with oxybutynin.

AND

- The patient has had a documented side effect, allergy, or treatment failure with 2 preferred long-acting agents. If a medication has an AB rated generic there must have also been a trial of the generic formulation.

Oxytrol

- The patient has a medical necessity for a transdermal formulation (ex. dysphasia, inability to take oral medications).

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